Re: Cervical Carcinoma and Human Papillomavirus: On the Road to Preventing a Major Human Cancer

In an editorial in the February 21, 2001, issue of the Journal, H. zur Hausen *(1)* reviewed historical aspects of the field of human papillomaviruses (HPVs) and cervical cancer. In his final remarks, he described an unjustified delay in HPV vaccine development by industrial partners. In his view, this delay was related to the cautious interpretation of the early results that was taken by epidemiologists at the International Agency for Research on Cancer (IARC) and elsewhere. Some of the implications of the editorial are in our view too negative.

HPV research has benefited from a remarkable collaboration between epidemiologists and basic scientists. Given the right biomarkers and testing systems, in slightly more than a decade, it has been possible to demonstrate a strong, specific, and universal association between HPV infection and risk of human cervical cancer. Studies based on populations are the only ones capable of estimating the natural history parameters that are essential to plan, conduct, and evaluate preventive strategies. These strategies refer equally to the fundamental and rapidly growing field of HPV-based screening programs *(2)* as well as to HPV vaccination trials.

The time lag that was required to characterize the association can be largely traced to the limitations of the early HPV-DNA tests. Some of the well-designed epidemiologic studies carried out during the late 1980s provided inconsistent evidence because of the use of assays with low specificity and sensitivity *(3,4).* Progress in HPV detection systems has been remarkable and, by the late 1990s, HPV was proposed as the first "necessary, nonsufficient" cause of a human cancer ever identified *(5).* In 1992 and 1995, respectively, one scientific publication *(6)* and a monograph *(7)* produced by the IARC, with an international participation of close to 60 external scientists, reviewed the field and considered HPV16 and HPV18 to be human carcinogens.

The inference that the biotechnology industry was reluctant to invest in HPV vaccine development largely because of IARC's cautious views in the late 1980s gives undue weight to this single element. Academic arguments are one (albeit necessary) component of a complex decision-making process. Market considerations aside, identifying the appropriate technologies was probably also a strong determinant of industrial decisions. As noted in the editorial *(1),* the virus-like particle technology that is used both as the basis for most candidate vaccines and as a way to measure immune response to vaccination was not in place until the early 1990s, just after the development of validated HPV detection systems required for clinical vaccination trials.

The biomedical literature has many examples of false starts in carcinogen discoveries. Rather than delaying progress in the field, epidemiologists have kept a fast research pace, providing the evidence required and implementing novel preventive efforts. In the immediate future, collaboration across disciplines will have an increasing relevance. Highly sophisticated technologies are already being proposed for population screening and individual diagnosis. In this bright perspective, mutual contributions and expertise are more necessary than ever.

In conclusion, we certainly share Professor zur Hausen's view that HPV is the eminently preventable cause of cervical cancer, but in the late 1980s it seemed prudent to many to wait until consistent epidemiologic data supported the inferences from molecular biologic studies.

F. Xavier Bosch
Nubia Muñoz
Silvia de Sanjosé
Eduardo L. F. Franco
Douglas R. Lowy
Mark Schiffman
Silvia Franceschi
Susanne Krüger Kjaer
Chris J. L. M. Meijer
Ian H. Frazer
Jack Cuzick

References

(1) zur Hausen H. Cervical carcinoma and human papillomavirus: on the road to preventing a major human cancer [editorial]. J Natl Cancer Inst 2001;93:252–3.

(2) Cuzick J, Szarewski A, Terry G, Ho L, Hanby A, Maddox P, et al. Human papillomavirus testing in primary cervical screening. Lancet 1995;345:1533–6.

(3) Franco EL. The sexually transmitted disease model for cervical cancer: incoherent epidemiologic findings and the role of misclassification of human papillomavirus infection. Epidemiology 1991;2:98–106.

(4) Schiffman MH, Schatzkin A. Test reliability is critically important to molecular epidemiology: an example from studies of human papillomavirus infection and cervical neoplasia. Cancer Res 1994;54(7 Suppl):1944s–1947s.

(5) Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189:12–9.

(6) Munoz N, Bosch FX, Shah KV, Meheus A, editors. The epidemiology of human papillomavirus and cervical cancer. Lyon (France):

International Agency for Research on Cancer. IARC Sci Publ No. 119;1992.
(7) IARC Working Group. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: human papillomavirus. Lyon (France): International Agency for Research on Cancer. IARC Sci Publ Vol 64;1995.

NOTES

Affiliations of authors: F. X. Bosch, S. de Sanjosé, Institut Català d'Oncologia and Hospitalet Llobregat, Barcelona, Spain; N. Muñoz, S. Franceschi, International Agency for Research on Cancer, Lyon, France; E. L. F. Franco, McGill University, Montréal, PQ, Canada; D. R. Lowy, Laboratory of Cellular Oncology, National Cancer Institute, Bethesda, MD; M. Schiffman, Environmental Epidemiology Branch, National Cancer Institute, Rockville, MD; S. K. Kjaer, Danish Cancer Society, Copenhagen, Denmark; C. J. L. M. Meijer, University Hospital Vrije Universiteit, Amsterdam, The Netherlands; I. H. Frazer, Center for Immunology and Cancer Research, Brisbane, Australia; J. Cuzick, Imperial Cancer Research Fund, London, U.K.

Correspondence to: F. Xavier Bosch, M.D., Institut Català d'Oncologia, Servei de'Epidemiologia i Registre del Càncer, Av. Gran Via s/n, Km. 2.7, E-08907 L'Hospitalet de Llobregat, Barcelona, Spain (e-mail: x.bosch@ico.scs.es).

RESPONSE

I appreciate the comments of Dr. Bosch and his colleagues. The final remarks of the cited editorial included the following sentences: ". . . it was stated in a publication of the International Agency for Research on Cancer in 1989 that 'the available data, although suggestive, do not allow further inferences on causality' [*(1)*]. . . . In the personal experience of this author, up to this period it has not been possible to convince the pharmaceutical industry to consider the initiation of vaccination programs against high-risk HPV infections and, in all likelihood, several years have been lost. If we calculate an annual incidence rate of 400 000 cases per year globally [*(2)*], this delay may turn out to be costly."

I certainly agree with Bosch et al. that, in the end, "HPV research has benefited from a remarkable collaboration between epidemiologists and basic scientists." Concerning early industrial involvement, however, one should not underestimate the role of statements from co-workers of internationally well-known epidemiology centers [*see (1)*], particularly if underlined by numerous presentations at international meetings and presented in an official scientific publication of the respective center.

The virus-like particle technology was not (and even today is not) the sole option for HPV vaccines in the late 1980s. In addition, it has been stated much earlier than in the late 1990s that HPV represents a "necessary, nonsufficient cause" of a human cancer *(3,4)*. Besides these small inconsistencies in the correspondence of Bosch et al., however, it has not been my intention to blame specific scientists for a potentially costly delay in HPV vaccine development. We all should be pleased that, at least in the foreseeable future, HPV vaccines are clearly on their way to a broad application in groups at risk for cervical cancer. In my opinion, the only lesson we can take from this history is to argue for an early commitment of scientists to prevention and control of common human diseases (in this case, a deadly cancer), if there exists a reasonable basis for the involvement of a specific agent. For cancer of the cervix, substantial evidence was available by the end of 1987, as summarized in the editorial.

HARALD ZUR HAUSEN

REFERENCES

(1) Bosch FX, Munoz N. Human papillomavirus and cervical neoplasia: a critical review of the epidemiological evidence. IARC Sci Publ 1989;94:135–51.
(2) Parkin DM, Pisani P, Ferlay J. Estimates of worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999;80:827–41.
(3) zur Hausen H. Papillomaviruses in anogenital cancer as a model to understand the role of viruses in human cancers. Cancer Res 1989; 49:4677–81.
(4) zur Hausen H. Are human papillomavirus infections not necessary or sufficient causal factors for invasive cancer of the cervix? [letter]. Int J Cancer 1995;63:315–6.

NOTE

Correspondence to: Harald zur Hausen, M.D., Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany (e-mail: zurhausen@dkfz-heidelberg.de).